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(54) Title: HUMAN CELL SURFACE RECEPTOR PROTEINS																							
(57) Abstract <p>The invention provides human cell surface receptor proteins (HCSRPs) and polynucleotides which identify and encode HCSRPs. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of HCSRPs.</p>																							

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HUMAN CELL SURFACE RECEPTOR PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human cell surface receptor proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative disorders, immune system disorders, infections, and neuronal disorders.

5

BACKGROUND OF THE INVENTION

The term receptor describes proteins that specifically recognize other molecules. The category is broad and includes proteins with a variety of functions. The bulk of receptors are cell surface proteins which bind extracellular ligands and produce cellular responses in the areas of growth, differentiation, endocytosis, exocytosis and immune response. Central to the function of cell surface receptors is the capacity to adhere or bind to other proteins or ligands through special functional domains.

Cell surface receptors are typically integral plasma membrane proteins. These receptors recognize hormones such as catecholamines; peptide hormones; growth and differentiation factors; small peptide factors such as thyrotropin releasing hormone; galanin, somatostatin, and tachykinins; and circulatory system-borne signaling molecules. Cell surface receptors on immune system cells recognize antigens, antibodies, and major histocompatibility complex (MHC)-bound peptides. Other cell surface receptors bind ligands to be internalized by the cell. This receptor-mediated endocytosis functions in the uptake of low density lipoproteins (LDL), transferrin, glucose- or mannose-terminal glycoproteins, galactose-terminal glycoproteins, immunoglobulins, phosphovitellogenins, fibrin, proteinase-inhibitor complexes, plasminogen activators, and thrombospondin (Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York NY, p. 723; and Mikhailenko, I. et al. (1997) *J. Biol. Chem.* 272:6784-6791).

Many growth factor receptors, including receptors for epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, as well as the growth modulator α -thrombin, contain intrinsic protein kinase activities. When growth factor binds to the receptor, it triggers the autophosphorylation of a serine, threonine, or tyrosine residue on the receptor. These phosphorylated sites are recognition sites for the binding of other cytoplasmic signaling proteins. These proteins participate in signaling pathways that eventually link the initial receptor activation at the cell surface to the activation of a specific intracellular target molecule. In the case of tyrosine residue autophosphorylation, these signaling proteins contain a common domain referred to as a src homology 2 (SH2) domain. SH2 domains are found in a variety of signaling molecules and oncogenic proteins

such as phospholipase C- γ , Ras GTPase activating protein, and pp60^{c-src} (Lowenstein, E.J. et al. (1992) Cell 70:431-442).

G-protein coupled receptors (GPCRs)

G-protein coupled receptors (GPCRs) are integral membrane proteins characterized by the presence of seven hydrophobic transmembrane domains which span the plasma membrane and form a bundle of antiparallel alpha (α) helices. These proteins range in size from under 400 to over 1000 amino acids (Strosberg, A.D. (1991) Eur. J. Biochem. 196:1-10; Coughlin, S.R. (1994) Curr. Opin. Cell Biol. 6:191-197). The amino-terminus of the GPCR is extracellular, of variable length and often glycosylated; the carboxy-terminus is cytoplasmic and generally phosphorylated. Extracellular loops of the GPCR alternate with intracellular loops and link the transmembrane domains. The most conserved domains of GPCRs are the transmembrane domains and the first two cytoplasmic loops. The transmembrane domains account for structural and functional features of the receptor. In most cases, the bundle of alpha helices forms a binding pocket. In addition, the extracellular N-terminal segment or one or more of the three extracellular loops may also participate in ligand binding. Ligand binding activates the receptor by inducing a conformational change in intracellular portions of the receptor. The activated receptor, in turn, interacts with an intracellular heterotrimeric guanine nucleotide binding (G) protein complex which mediates further intracellular signaling activities, generally the production of second messengers such as cyclic AMP (cAMP), phospholipase C, inositol triphosphate or ion channel proteins (Baldwin, J.M. (1994) Curr. Opin. Cell Biol. 6:180-190).

One group of GPCRs are the rhodopsin-like GPCRs that transmit extracellular signals of diverse natures including hormones, neurotransmitters and light. Rhodopsin is a photosensitive GPCR in the vertebrate eye. Rhodopsin, which defines a conserved subfamily of GPCRs found in animal retinas, is about 350 amino acids in length. In vertebrates, rhodopsin molecules are embedded in membranous stacks found in photoreceptor (rod) cells. Each rhodopsin molecule responds to a photon of light by triggering a decrease in cGMP levels which leads to the closure of plasma membrane sodium channels. In this manner, a visual signal is converted to a neural impulse. Other rhodopsin-like GPCRs are directly involved in responding to neurotransmitters. These GPCRs include the receptors for adrenaline (adrenergic receptors), acetylcholine (muscarinic receptors), adenosine, galanin, and glutamate (N-methyl-D-aspartate/NMDA receptors). (Reviewed in Watson, S. and Arkinstall, S. (1994) The G-Protein Linked Receptor Facts Book. Academic Press, San Diego, CA, pp. 7-9, 19-22, 32-35, 130-131, 214-216, 221-222; Habert-Ortoli, E. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9780-9783.)

The somatostatin receptor type 4 is another example of a rhodopsin-like GPCR. It is one of several high affinity receptors for somatostatin, a tetrapeptide that inhibits the secretion of growth

hormone from the anterior pituitary. Expression of particular somatostatin receptors has been linked to the efficacy of drug therapy in specific endocrine tumors (Kubota, A. et al. (1994) J. Clin. Invest. 93:1321-1325).

Another rhodopsin-like GPCR is the prostanoid EP1 receptor that recognizes prostanoids such as prostaglandin to mediate a variety of physiological functions including cardiovascular and immune responses. EP1 receptors have a role in the contraction and relaxation of smooth muscle and can activate the phosphoinositide pathway (Watson, *supra*, pp. 239-251). The prostanoid DP receptor is another rhodopsin-like GPCR that is specific for prostaglandin D2 (PGD2). Expression of the DP receptor has been localized to the mammalian brain and eye tissues and upon activation facilitates elevation of intracellular cAMP and Ca²⁺ mobilization but does not generate inositol 1,4,5-triphosphate (Boie, Y. et al. (1995) J. Biol. Chem. 270:18910-18916; Gerashchenko, D. et al. (1998) J. Neurochem. 71:937-945).

Still another rhodopsin-like GPCR is the endothelin receptor that plays a role in cardiovascular system regulation through endothelins. Endothelins are potent vasoconstrictors that can stimulate cardiac and smooth muscle contraction as well as stimulate secretion in tissues such as kidney, liver and adrenals. Endothelin receptors may have a role in the brain, where they are also found, and there is evidence that endothelins may be associated with pathophysiological conditions such as stress (Watson, *supra*, pp. 111-116).

The secretin receptor is an example of a unique GPCR that responds to secretin, a peptide hormone that stimulates the secretion of enzymes and ions in the pancreas and small intestine (Watson, *supra*, pp. 278-283). Secretin receptors are about 450 amino acids in length and are found in the plasma membrane of gastrointestinal cells. Binding of secretin to its receptor stimulates the production of cAMP. An unusual member of the secretin receptor family has been identified from a neuroectodermal cDNA library (Baud, V. et al. (1995) Genomics 26:334-344). This receptor, EMR1 (EGF-like, mucin-like hormone receptor), is 886 amino acids in length and contains six epidermal growth factor (EGF)-like modules at the N-terminus followed by a serine/threonine rich domain. The latter feature is characteristic of mucin-like integral membrane adhesive proteins.

Other GPCRs have been identified which play a role in the immune response. For example, a new subfamily of GPCRs has been identified from a human monocyte (HM) cDNA library (Nomura, H. et al. (1993) Int. Immunol. 5:1239-1249). Most of these GPCRs likely bind to cytokines and other leukocytic signaling molecules. One of these GPCRs, HM74, is particularly unusual in that its N-terminus does not contain N-glycosylation sites.

The thrombin receptors (TRs) have GPCR activity and are activated by the ligand α -thrombin. Through TR-mediated signal transduction pathways, α -thrombin induces production of IL-8 and IL-6

in cultured monocytes and endothelial cells (Johnson, K. et al. (1998) *J. Immunol.* 160:5130-5135). Conversely, α -thrombin inhibits the action of IL-6, leukemia inhibitory factor, and ciliary neurotrophic factor in chinese hamster lung fibroblasts (Bhat, G.J. et al. (1998) *Arch. Biochem. Biophys.* 350:307-314). In addition, when α -thrombin binds to the TR it proteolytically cleaves 40 amino acids from the N-terminus of the receptor. The cleaved peptide is termed the thrombin receptor agonist peptide and acts as a tethered ligand for the TR to increase the potency of the thrombin-derived signal (Hou, L. Et al. (1998) *J. Periodontal Res.* 33:205-211; Johnson, et al. supra).

GPCR mutations, which may cause loss of function or constitutive activation, have been associated with numerous human diseases (Coughlin, supra). For instance, retinitis pigmentosa may arise from mutations in the rhodopsin gene. Parma, J. et al. (1993, *Nature* 365:649-651) report that somatic activating mutations in the thyrotropin receptor cause hyperfunctioning thyroid adenomas and suggest that certain GPCRs susceptible to constitutive activation may behave as protooncogenes.

Cytokine Receptors

Cytokines comprise a family of signaling molecules that modulate the immune system and the inflammatory response. Cytokines are usually secreted by leukocytes, or white blood cells, in response to injury or infection. However, other tissues are capable of secreting cytokines in response to disease or other physiologic perturbations. Cytokines function as growth and differentiation factors that act primarily on cells of the immune system such as lymphocytes, monocytes, and granulocytes. Like other signaling molecules, cytokines bind to specific plasma membrane receptors and trigger intracellular signal transduction pathways which regulate gene expression, cell proliferation, and cell differentiation.

Erythropoietin (EPO) is an unusual cytokine that is produced not by leukocytes, but instead by the kidney or liver. EPO stimulates erythroid precursors to differentiate into red blood cells. EPO also stimulates the production of platelets. The EPO receptor is a single-pass transmembrane protein of about 500 amino acids, the intracellular domain of which associates with JAK2 kinase. Activated EPO receptor stimulates the phosphorylation activity of JAK2 which triggers gene transcription and mitogenesis. (Reviewed in Callard, R. and Gearing, A. (1994) The Cytokine Facts Book, Academic Press, San Diego, CA, pp.114-118.)

Immunoglobulin Domain Receptors

Immune system and related cell surface receptor proteins have hallmark functional domains (for example the Immunoglobulin (Ig) domain) with similar functionality in a wide array of receptor types. The human immune system is responsible for combating infectious agents contracted from the environment. One critical component of the immune system are highly specialized molecules called immunoglobulins (Ig) or antibodies that can recognize and bind to foreign antigens, thereby

facilitating their elimination. Characteristic features of immunoglobulins include their structural motifs that include regions for membrane attachment, antigen recognition (variable (V) regions), and polymerization. Polymerized immunoglobulins such as glandularly secreted IgA and IgM must undergo transcellular transport, a process mediated by the poly-immunoglobulin (poly-Ig) receptor.

5 The poly-Ig receptor is itself a member of the immunoglobulin superfamily having homology to the variable (V) region of immunoglobulins (Hood, L. et al. (1985) Cell 40:225-229). Like all immunoglobulin superfamily members, poly-Ig receptor is involved in adhesion or binding to other proteins through the conserved immunoglobulin-like domain. This Ig domain is comprised of antiparallel β sheets joined by a disulfide bond in an arrangement called the Ig fold. Members of the

10 Ig superfamily include T-cell receptors, MHC proteins, CD4, CD8, and CD 28 cell surface proteins, and antibodies.

Immunoglobulins, or antibodies, are the central components of the humoral immune response. IgG, the most common class of immunoglobulin in the circulation, can be described in terms of two main functional domains. Antigen recognition is mediated by the Fab (antigen binding fragment)

15 region of the IgG, while effector functions are mediated by the Fc (crystallizable fragment) region. Binding of IgG to an antigen, such as a bacterium, triggers the destruction of the antigen by phagocytic white blood cells, such as macrophages and neutrophils. These cells express cell surface receptors that specifically bind to the IgG Fc region and allow the phagocytic cells to engulf, ingest, and degrade the IgG-bound antigen. The IgG Fc receptors expressed by phagocytic cells are single-

20 pass transmembrane glycoproteins of about 400 amino acids (Sears, D. W. et al. (1990) J. Immunol. 144:371-378). The extracellular portion of the IgG Fc receptor typically contains two or three Ig domains.

T cells play a dual role in the immune system as effectors and regulators, coupling antigen recognition with the transmission of signals that induce cell death in infected cells and stimulate other

25 immune cells. Although T cells collectively recognize a wide range of different antigens, a clonal line of T cells can only recognize a single antigen. Moreover, the antigen must be presented to the T cell receptor (TCR) as a peptide complexed with a major histocompatibility molecule (MHC) on the surface of an antigen-presenting cell. The TCR on most T cells consists of two polypeptide subunits, α and β , which are immunoglobulin-like integral membrane glycoproteins of similar molecular

30 weight. The TCR α and TCR β subunits have an extracellular domain containing both variable and constant regions, a transmembrane domain that traverses the membrane once, and a short intracellular domain (Saito, H. et al. (1984) Nature 309:757-762). The genes for the TCR subunits are constructed through somatic rearrangement of different gene segments. Interaction of antigen in the proper MHC context with the TCR initiates signaling cascades that induce the proliferation, maturation, and

function of cellular components of the immune system (Weiss, A. (1991) *Annu. Rev. Genet.* 25: 487-510). Rearrangements in TCR genes and alterations in TCR expression have been noted in lymphomas, leukemias, autoimmune disorders, and immunodeficiency disorders (Aisenberg, A.C. et al. (1985) *N. Engl. J. Med.* 313:529-533; Weiss, *supra*; and Olive, *supra*). Immunizations with
5 peptides derived from TCRs are effective treatment for some human T-cell-mediated autoimmune disease and in animal models of such illnesses, in particular, rheumatoid arthritis (Bridges, S.L. and Moreland, L.W. (1998) *Rheum. Dis. Clin. North Am.* 24:641-650).

The discovery of new human cell surface receptor proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis,
10 prevention, and treatment of cell proliferative disorders, immune system disorders, infections, and neuronal disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, human cell surface receptor
15 proteins, referred to collectively as "HCSRPs" and individually as "HCSRPs-1," "HCSRPs-2," "HCSRPs-3," "HCSRPs-4," "HCSRPs-5," "HCSRPs-6," "HCSRPs-7," "HCSRPs-8," "HCSRPs-9," "HCSRPs-10," "HCSRPs-11," "HCSRPs-12," and "HCSRPs-13." In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof. The invention also includes a polypeptide
20 comprising an amino acid sequence that differs by one or more conservative amino acid substitutions from an amino acid sequence selected from the group consisting of SEQ ID NO:1-13.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-13 and fragments thereof. The invention also provides an isolated and purified polynucleotide
25 encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof.

30 Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence

selected from the group consisting of SEQ ID NO:1-13 and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of: (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:14-26 and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:14-26 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:14-26 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-13. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing a polynucleotide of the invention under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-13 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of HCSR, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of HCSR, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-13 and fragments thereof.

5

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HCSR.

10 Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of HCSR.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was
15 cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding HCSR were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze HCSR, along with applicable descriptions, references, and threshold parameters.

20

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing
25 particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a
30 reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be

used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"HCSR" refers to the amino acid sequences of substantially purified HCSR obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

10 The term "agonist" refers to a molecule which intensifies or mimics the biological activity of HCSR. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of HCSR either by directly interacting with HCSR or by acting on components of the biological pathway in which HCSR participates.

An "allelic variant" is an alternative form of the gene encoding HCSR. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding HCSR include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as HCSR or a polypeptide with at least one functional characteristic of HCSR. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HCSR, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding HCSR. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HCSR. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of HCSR is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine.

Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of HCSR. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of HCSR either by directly interacting with HCSR or by acting on components of the biological pathway in which HCSR participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind HCSR polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the

complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HCSRPs, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HCSRPs or fragments of HCSRPs may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded

as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
5	Asn	Asp, Gln, His
	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
10	Gly	Ala
	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
15	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
20	Tyr	His, Phe, Trp
	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of HCSR or the polynucleotide encoding HCSR which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues

in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification,

5 including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:14-26 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:14-26, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:14-26 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:14-26 from related
10 polynucleotide sequences. The precise length of a fragment of SEQ ID NO:14-26 and the region of SEQ ID NO:14-26 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-13 is encoded by a fragment of SEQ ID NO:14-26. A fragment of SEQ ID NO:1-13 comprises a region of unique amino acid sequence that specifically identifies
15 SEQ ID NO:1-13. For example, a fragment of SEQ ID NO:1-13 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-13. The precise length of a fragment of SEQ ID NO:1-13 and the region of SEQ ID NO:1-13 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

20 The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization
25 assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to
30 one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and
5 therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in
10 Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

15 Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis
20 programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST
25 programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

30 *Penalty for mismatch: -2*

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention

include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, 5 denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative 10 of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C₀t or R₀t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid 15 support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune 20 disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable 25 polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of HCSR. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HCSR.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, 30 polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably

linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which
5 comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding HCSRPs, their complements, or fragments
10 thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target
15 DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100,
20 or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold
25 Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

30 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the

PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, *supra*. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HCSRPs, or fragments thereof, or HCSRPs itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a

protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide
5 containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which
10 they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers,
15 microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic
20 acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently
25 transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-
30 1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding

polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene
 5 between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having
 10 at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

15

THE INVENTION

The invention is based on the discovery of new human cell surface receptor proteins (HCSRPs), the polynucleotides encoding HCSRPs, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative disorders, immune system disorders, infections, and
 20 neuronal disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding HCSRPs. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each HCSRPs were identified, and column 4 shows the cDNA
 25 libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each HCSRPs and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention:
 30 column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods used to characterize each polypeptide through sequence homology and protein motifs. In

particular, the amino acid sequence of SEQ ID NO:1 from about amino acid residue 30 to about 81 is distinct from the tethered ligand thrombin receptor agonist peptide of the N-terminus of the human thrombin receptor and the amino acid sequence of SEQ ID NO:2 from about amino acid residue 115 to about 140 is distinct from the C-terminus joining and constant regions of the human TCR α subunit.

5 The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding HCSR. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:14-26 and to distinguish between SEQ ID NO:14-26 and related polynucleotide sequences. The
10 polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express HCSR as a fraction of total tissues expressing HCSR. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing HCSR as a fraction of total tissues expressing HCSR. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of HCSR in cancer, autoimmune and inflammatory
15 response, and in lung, thymus, bladder, seminal vesicle, and penile tissues, and in rheumatoid arthritis. In addition, SEQ ID NO: 14 is expressed primarily in tumor-associated epithelial tissues and SEQ ID NO: 15 is expressed primarily in growth- and tumor-associated epithelial tissues and in immune response tissues.

 The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries
20 from which cDNA clones encoding HCSR were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

 The invention also encompasses HCSR variants. A preferred HCSR variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid
25 sequence identity to the HCSR amino acid sequence, and which contains at least one functional or structural characteristic of HCSR.

 The invention also encompasses polynucleotides which encode HCSR. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:14-26, which encodes HCSR.

30 The invention also encompasses a variant of a polynucleotide sequence encoding HCSR. In particular, such a variant polynucleotide sequence will have at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HCSR. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID

NO:14-26 which has at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:14-26. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of HCSR.

5 It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HCSR, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These
10 combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HCSR, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode HCSR and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring HCSR under appropriately
15 selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HCSR or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the
20 nucleotide sequence encoding HCSR and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode HCSR and HCSR derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the
25 synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HCSR or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID
30 NO:14-26 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of

the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HCSR_P may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060.) Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence
5 into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the
10 emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

15 In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode HCSRPs may be cloned in recombinant DNA molecules that direct expression of HCSRPs, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express HCSRPs.

20 The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HCSRPs-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction
25 sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding HCSRPs may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.)
30 Alternatively, HCSRPs itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HCSRPs, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other

proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.)

The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing.
5 (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active HCSR, the nucleotide sequences encoding HCSR or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding
10 sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HCSR. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding HCSR. Such signals include the ATG initiation codon and adjacent sequences,
15 e.g. the Kozak sequence. In cases where sequences encoding HCSR and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and
20 initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HCSR and appropriate transcriptional and translational
25 control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

30 A variety of expression vector/host systems may be utilized to contain and express sequences encoding HCSR. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or

tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HCSR. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HCSR can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPT1 plasmid (Life Technologies). Ligation of sequences encoding HCSR into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509.) When large quantities of HCSR are needed, e.g. for the production of antibodies, vectors which direct high level expression of HCSR may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HCSR. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Bitter, G.A. et al. (1987) *Methods Enzymol.* 153:516-544; and Scorer, C.A. et al. (1994) *Bio/Technology* 12:181-184.)

Plant systems may also be used for expression of HCSR. Transcription of sequences encoding HCSR may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., *The McGraw Hill Yearbook of Science and Technology* (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding HCSR may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain

infective virus which expresses HCSRP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

5 Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

10 For long term production of recombinant proteins in mammalian systems, stable expression of HCSRP in cell lines is preferred. For example, sequences encoding HCSRP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media
15 before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These
20 include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* and *apv* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, J. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat*
25 confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins
30 (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is

also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HCSRП is inserted within a marker gene sequence, transformed cells containing sequences encoding HCSRП can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HCSRП under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding HCSRП and that express HCSRП may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of HCSRП using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HCSRП is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding HCSRП include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HCSRП, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HCSRП may be cultured under

conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HCSRPs may be designed to contain signal sequences which
5 direct secretion of HCSRPs through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or
10 "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

15 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HCSRPs may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HCSRPs protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of HCSRPs activity. Heterologous protein and
20 peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-
25 chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HCSRPs encoding sequence and the heterologous protein sequence, so that HCSRPs may be cleaved away from the heterologous moiety following purification.
30 Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HCSRPs may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These

systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

Fragments of HCSRП may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of HCSRП may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HCSRП and human cell surface receptor proteins. In addition, the expression of HCSRП is closely associated with lung, thymus, bladder, seminal vesicle, and penile tissues, with rheumatoid arthritis, and with inflammation, cancer, and the nervous system. Therefore, HCSRП appears to play a role in cell proliferative disorders, immune system disorders, infections, and neuronal disorders. In the treatment of disorders associated with increased HCSRП expression or activity, it is desirable to decrease the expression or activity of HCSRП. In the treatment of disorders associated with decreased HCSRП expression or activity, it is desirable to increase the expression or activity of HCSRП.

Therefore, in one embodiment, HCSRП or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HCSRП. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune system disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome,

- episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus,
- 5 systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; an infection caused by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepatitis virus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus,
- 10 picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, or togavirus; an infection caused by a bacterial agent classified as pneumococcus, staphylococcus, streptococcus, bacillus, corynebacterium, clostridium, meningococcus, gonococcus, listeria, moraxella, kingella, haemophilus, legionella, bordetella, gram-negative enterobacterium including shigella, salmonella, or campylobacter, pseudomonas, vibrio, brucella, francisella, yersinia, bartonella, norcardium, actinomyces,
- 15 mycobacterium, spirochaetale, rickettsia, chlamydia, or mycoplasma; an infection caused by a fungal agent classified as aspergillus, blastomyces, dermatophytes, cryptococcus, coccidioides, malassezia, histoplasma, or other fungal agents causing various mycoses; an infection caused by a parasite classified as plasmodium or malaria-causing, parasitic entamoeba, leishmania, trypanosoma, toxoplasma, pneumocystis carinii, intestinal protozoa such as giardia, trichomonas, tissue nematodes
- 20 such as trichinella, intestinal nematodes such as ascaris, lymphatic filarial nematodes, trematodes such as schistosoma, or cestodes such as tapeworm; and a neuronal disorder such as akathisia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, cerebral neoplasms, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis,
- 25 neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder.

In another embodiment, a vector capable of expressing HCSR or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HCSR including, but not limited to, those described above.

- 30 In a further embodiment, a pharmaceutical composition comprising a substantially purified HCSR in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HCSR including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of HCSR may be

administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HCSRП including, but not limited to, those listed above.

In a further embodiment, an antagonist of HCSRП may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HCSRП. Examples of such disorders include, but are not limited to, those cell proliferative disorders, immune system disorders, 5 infections, and neuronal disorders described above. In one aspect, an antibody which specifically binds HCSRП may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express HCSRП.

In an additional embodiment, a vector expressing the complement of the polynucleotide 10 encoding HCSRП may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HCSRП including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made 15 by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HCSRП may be produced using methods which are generally known in the art. In particular, purified HCSRП may be used to produce antibodies or to screen libraries of 20 pharmaceutical agents to identify those which specifically bind HCSRП. Antibodies to HCSRП may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit 25 dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HCSRП or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral 30 gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Cornebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HCSRП have an amino acid sequence consisting of at least about 5 amino acids, and generally will

consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of HCSRPs amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to HCSRPs may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) *Nature* 256:495-497; Kozbor, D. et al. (1985) *J. Immunol. Methods* 81:31-42; Cote, R.J. et al. (1983) *Proc. Natl. Acad. Sci. USA* 80:2026-2030; and Cole, S.P. et al. (1984) *Mol. Cell Biol.* 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Neuberger, M.S. et al. (1984) *Nature* 312:604-608; and Takeda, S. et al. (1985) *Nature* 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HCSRPs-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotype composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) *Proc. Natl. Acad. Sci. USA* 88:10134-10137.)

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:3833-3837; Winter, G. et al. (1991) *Nature* 349:293-299.)

Antibody fragments which contain specific binding sites for HCSRPs may also be generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) *Science* 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between HCSRPs and its

specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering HCSRPs is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HCSRPs. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of HCSRPs-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HCSRPs, represents the average affinity, or avidity, of the antibodies for HCSRPs. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HCSRPs epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HCSRPs-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HCSRPs, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of HCSRPs-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding HCSRPs, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding HCSRPs may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding HCSRPs. Thus, complementary molecules or fragments may be used to modulate HCSRPs activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding HCSRPs.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding
5 HCSR. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding HCSR can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding HCSR. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules
10 until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or
15 regulatory regions of the gene encoding HCSR. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances
20 using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of
25 RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding HCSR.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by
30 scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary

oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis.

5 Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding HCSRPs. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

10 RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine,
15 and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient.

20 Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and
25 monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HCSRPs, antibodies to HCSRPs, and mimetics, agonists, antagonists, or inhibitors of HCSRPs. The compositions
30 may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any

number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable
5 pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using
10 pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after
15 grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents
20 may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.
25 Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or
30 starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's

solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of HCSRPs, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HCSRPs or fragments thereof, antibodies of HCSRPs, and agonists, antagonists or inhibitors of HCSRPs, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such

as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and
5 animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the
10 subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4
15 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μ g to 100,000 μ g, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.
20 Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind HCSRPs may be used for the
25 diagnosis of disorders characterized by expression of HCSRPs, or in assays to monitor patients being treated with HCSRPs or agonists, antagonists, or inhibitors of HCSRPs. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for HCSRPs include methods which utilize the antibody and a label to detect HCSRPs in human body fluids or in extracts of cells or tissues. The antibodies may be used with or
30 without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring HCSRPs, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HCSRPs expression.

Normal or standard values for HCSRП expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to HCSRП under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of HCSRП expressed
5 in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding HCSRП may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect
10 and quantify gene expression in biopsied tissues in which expression of HCSRП may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HCSRП, and to monitor regulation of HCSRП levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding HCSRП or closely related molecules may be used
15 to identify nucleic acid sequences which encode HCSRП. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding HCSRП, allelic variants, or related sequences.

20 Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the HCSRП encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:14-26 or from genomic sequences including promoters, enhancers, and introns of the HCSRП gene.

Means for producing specific hybridization probes for DNAs encoding HCSRП include the
25 cloning of polynucleotide sequences encoding HCSRП or HCSRП derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ³²P or ³⁵S, or by enzymatic labels,
30 such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding HCSRП may be used for the diagnosis of disorders associated with expression of HCSRП. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal

- hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid,
- 5 penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune system disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic
- 10 dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation,
- 15 myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and
- 20 myeloma; an infection caused by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, or togavirus; an infection caused by a bacterial agent classified as pneumococcus, staphylococcus, streptococcus, bacillus, corynebacterium, clostridium, meningococcus, gonococcus, listeria, moraxella, kingella,
- 25 haemophilus, legionella, bordetella, gram-negative enterobacterium including shigella, salmonella, or campylobacter, pseudomonas, vibrio, brucella, francisella, yersinia, bartonella, norcardium, actinomyces, mycobacterium, spirochaetale, rickettsia, chlamydia, or mycoplasma; an infection caused by a fungal agent classified as aspergillus, blastomyces, dermatophytes, cryptococcus, coccidioides, malassezia, histoplasma, or other fungal agents causing various mycoses; an infection
- 30 caused by a parasite classified as plasmodium or malaria-causing, parasitic entamoeba, leishmania, trypanosoma, toxoplasma, pneumocystis carinii, intestinal protozoa such as giardia, trichomonas, tissue nematodes such as trichinella, intestinal nematodes such as ascaris, lymphatic filarial nematodes, trematodes such as schistosoma, or cestodes such as tapeworm; and a neuronal disorder such as akathisia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder,

catatonia, cerebral neoplasms, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder. The polynucleotide sequences encoding HCSRП may be used in Southern or
5 northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered HCSRП expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HCSRП may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide
10 sequences encoding HCSRП may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HCSRП in the
15 sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of HCSRП, a normal or standard profile for expression is established. This may be accomplished by
20 combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HCSRП, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values
25 obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from
30 successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance

of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding
5 HCSRPs may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced *in vitro*. Oligomers will preferably contain a fragment of a polynucleotide encoding HCSRPs, or a fragment of a polynucleotide complementary to the polynucleotide encoding HCSRPs, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or
10 quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of HCSRPs include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) *J. Immunol. Methods* 159:235-244; Duplaa, C. et al. (1993) *Anal. Biochem.* 212:229-236.) The speed of quantitation of multiple samples may be
15 accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray
20 can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g.,
25 Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HCSRPs may be
30 used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355; Price,

C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the
5 Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding HCSRП on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

10 In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides
15 valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be
20 used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HCSRП, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a
25 solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HCSRП and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are
30 synthesized on a solid substrate. The test compounds are reacted with HCSRП, or fragments thereof, and washed. Bound HCSRП is then detected by methods well known in the art. Purified HCSRП can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HCSRП specifically compete with a test compound for binding HCSRП. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HCSRП.

5 In additional embodiments, the nucleotide sequences which encode HCSRП may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding
10 description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific
15 embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No. PF-0636 P, filed November 12, 1998], U.S. Ser. No. [Attorney Docket No. PF-0650 P, filed December 7, 1998], and U.S. Ser. No. 60/123,404 are hereby
20 expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some
25 tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

30 Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA

purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the
5 recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column
10 chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUEScript plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or
15 ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by *in vivo* excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge
20 Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a
25 high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

30 III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared

using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the
5 ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

10 The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools,
15 programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software
20 (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA
25 sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled
30 into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS,

DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:14-26. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7: Ausubel, 1995, *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding HCSR occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of HCSR Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:14-26 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other
5 primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

10 Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$,
15 and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2:
20 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar,
25 Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

30 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones

were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:14-26 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:14-26 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and

compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, *supra*.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the HCSRPEncoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HCSRPE. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HCSRPE. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HCSRPE-encoding transcript.

IX. Expression of HCSRPE

Expression and purification of HCSRPE is achieved using bacterial or virus-based expression systems. For expression of HCSRPE in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA

transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3).

Antibiotic resistant bacteria express HCSRП upon induction with isopropyl beta-D-

- 5 thiogalactopyranoside (IPTG). Expression of HCSRП in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HCSRП by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong
- 10 polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

- 15 In most expression systems, HCSRП is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham
- 20 Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HCSRП at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995,
- 25 supra, ch. 10 and 16). Purified HCSRП obtained by these methods can be used directly in the following activity assay.

X. Demonstration of HCSRП Activity

- An assay for HCSRП activity measures the expression of HCSRП on the cell surface. cDNA encoding HCSRП is transfected into an appropriate mammalian cell line. Cell surface proteins are
- 30 labeled with biotin as described (de la Fuente, M. A. et al. (1997) Blood 90:2398-2405). Immunoprecipitations are performed using HCSRП-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of HCSRП expressed on the cell surface.

An alternative assay for HCSRП activity is based on a prototypical assay for ligand/receptor-mediated modulation of cell proliferation. This assay measures the amount of newly synthesized DNA in Swiss mouse 3T3 cells expressing HCSRП. An appropriate mammalian expression vector containing cDNA encoding HCSRП is added to quiescent 3T3 cultured cells using transfection methods well known in the art. The transfected cells are incubated in the presence of [³H]thymidine and varying amounts of HCSRП ligand. Incorporation of [³H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a tritium radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold HCSRП ligand concentration range is indicative of receptor activity. One unit of activity per milliliter is defined as the concentration of HCSRП producing a 50% response level, where 100% represents maximal incorporation of [³H]thymidine into acid-precipitable DNA. (McKay, I. and Leigh, I., eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York, NY, p. 73.)

XI. Functional Assays

HCSRП function is assessed by expressing the sequences encoding HCSRП at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in

flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of HCSR on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HCSR and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HCSR and other genes of interest can be analyzed by northern analysis or microarray techniques.

10 XII. Production of HCSR Specific Antibodies

HCSR substantially purified using polyacrylamide gel electrophoresis (PAGE: see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the HCSR amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-HCSR activity by, for example, binding the peptide or HCSR to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

25 XIII. Purification of Naturally Occurring HCSR Using Specific Antibodies

Naturally occurring or recombinant HCSR is substantially purified by immunoaffinity chromatography using antibodies specific for HCSR. An immunoaffinity column is constructed by covalently coupling anti-HCSR antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing HCSR are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HCSR (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt

antibody/HCSRП binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HCSRП is collected.

XIV. Identification of Molecules Which Interact with HCSRП

HCSRП, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent.
5 (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HCSRП, washed, and any wells with labeled HCSRП complex are assayed. Data obtained using different concentrations of HCSRП are used to calculate values for the number, affinity, and association of HCSRП with the candidate molecules.

10 Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are
15 obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	14	2355971	LUNGNOT20	2355971F6 and 2355971H1 (LUNGNOT20)
2	15	2917059	THYMFET03	2917059F6, 2917059H1, and 2917059T6 (THYMFET03)
3	16	538181	LNODNOT02	538181H1 (LNODNOT02), 1437379F1 (PANCNOT08), 2945139F6 (BRAITUT23), SAJA00666R1, SAJA00920R1, SAJA00173F1, SAJA00783R1
4	17	1368760	SCORN02	1368760H1 and 1368760T6 (SCORN02), SAUB01170F1
5	18	1670669	BMARNOT03	1670669F6 and 1670669H1 (BMARNOT03), SAEA03216R1
6	19	2851578	BRSTTUT13	992052T1 (COLNNOT11), 1579409F1 (DUODNOT01), 1880543T6 (LEUKNOT03), 4088508H1 (LIVRNOT06), 2851578H1, 2851578X310F1, and 2851578X311F1 (BRSTTUT13)
7	20	3393757	LUNGNOT28	318405H1 (EOSIHET02), 2230506H1 (PROSNOT16), 4592475F6 (MASTTUT01), 3393757H1, 3393757X301D2, and 3393757X305B2 (LUNGNOT28), SZAH04055F1, SZAH01718F1
8	21	312256	LUNGNOT02	306245T6 (HEARNOT01), 312256H1 (LUNGNOT02), 4175078H1 (SINTNOT21), SCAA06277V1, SCAA02060V1, SCAA02643V1
9	22	1615704	BRAITUT12	1615704F6 (BRAITUT12), 1615704H1 (BRAITUT12), 1615704X13 (BRAITUT12), 1727857F6 (PROSNOT14), 3539783H1 (SEMNOT04)
10	23	1659465	URETTUT01	265886F1 (HNT2AGT01), 1441970R1 (THYRNOT03), 1522238X12 (BLADTUT04), 1659465H1 (URETTUT01), 2187904T6 (PROSNOT26), 3237635H1 (COLAUCT01)

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
11	24	2120743	BRSTNOT07	661461R6 (BRAINOT03), 1318546F6 (BLADNOT04), 1318694T1 (BLADNOT04), 2044109H1 (HIPONON02), 2120743F6 (BRSTNOT07), 2120743H1 (BRSTNOT07), SBIA06480D1, SBIA02214D1, SBIA05533D1, SBIA03320D1, SBIA10018D1, SBIA07320D1, SBIA00175D1
12	25	3344986	SPLNNOT09	138687F1 (LIVRNOT01), 138687X27C1 (LIVRNOT01), 169384X8 (BMARNOR02), 3344986H1 (SPLNNOT09)
13	26	3576503	BRONNOT01	2525456F6 (BRAITUT21), 2527260F6 (BRAITUT21), 3576503H1 (BRONNOT01), 3742127F6 (MENTNOT01)

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Motifs, Signature Sequences, and Protein Domains	Homologous Sequences	Analytical Methods
1	81	S21 T43		Signal peptide: M1-A22 Receptor signature: C12-R28	thrombin receptor g339677	BLAST MOTIFS BLOCKS PRINTS HMM
2	140	S20 S33 S49 S73 S61 T90	N88	Signal peptide: M1-G22 Receptor tyrosine kinase signature: R82-A99 Receptor signature: A99-C111	T cell receptor alpha chain g1223888	BLAST MOTIFS BLOCKS PRINTS HMM
3	358	T47 T65 T163 T228 T283 S299 T352		Ig domains: G91-G144; G184-A241 Signal peptide: M1-A25	IgG Fc receptor g583604	BLAST MOTIFS PFAM SPSCAN HMM

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Motifs, Signature Sequences, and Protein Domains	Homologous Sequences	Analytical Methods
4	201	T44 T131 T65 T167	N63	Glutamate receptor domain: M1-G170 GPCR/Neurotransmitter receptor signatures: T114-T122; M7-S26 L145-H155; F90-G103 Signal peptide: M1-G28	Glutamate receptor isoform g507827	BLAST MOTIFS PFAM PRINTS SPSCAN
5	117	T54 T75 S104		Cytokine receptor signature: D32-E93 Signal peptide: M1-W24 or M1-A25	EPO receptor isoform g553281	BLAST MOTIFS PROFILESKAN SPSCAN HMM
6	455	S22 S380 S53 T189 T206 S271 S281 T310 S430	N76 N207	Rhodopsin GPCR domain: G141-Y387 Rhodopsin signatures: F126-C150; N159-R180 L204-V226; A325-A349 F369-L395 Transmembrane domains: L291-T310; A128-C150	Rhodopsin-like GPCR/HM74 g219867	BLAST MOTIFS PROFILESKAN PFAM BLOCKS PRINTS HMM

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Motifs, Signature Sequences, and Protein Domains	Homologous Sequences	Analytical Methods
7	453	S71 T418 S87 T244 T340 S428 T433 T438 T449	N73 N77 N183 N247 N252	Secretin signatures: V155-K179; I218-L241 K261-L286; W303-K328 A377-L398 Transmembrane domains: M159-L177; I302-V322 Y378-L398	Secretin-like GPCR/EMR1 g784994	BLAST MOTIFS BLOCKS PRINTS HMM
8	442	T53 S103 S115 T155 S190 T176 T233 T310 S368 Y241 Y329	N67 N101 N113 N165 N304 N308 N432	Transmembrane domain: A375-I394 Signal peptide: M1-G44 Immunoglobulin domains: G57-L126; G159-V222 G260-A315	Immuno- superfamily protein B12 g3779242	HMM BLAST PFAM SPSCAN BLOCKS-DOMO
9	382	S152 S199 T267 T324 S29	N65 N178 N322	Transmembrane domains: M1-I21; L289-F306 Signal peptide M1-S29 Somatostatin receptor: L237-L254 2 Poly-Immunoglobulin receptor: F9-P46; E86-P123 P104-F134; V259-F306 L283-A320		HMM SPSCAN PRINTS BLOCKS-DOMO

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Motifs, Signature Sequences, and Protein Domains	Homologous Sequences	Analytical Methods
10	257	S162 S7 T228		Transmembrane domain: Y187-L210 Signal peptide: M1-S33 Endothelin-A receptor: Q236-T255 2 Poly-Immunoglobulin receptor: Y91-R138; Y170-L217		HMM SPSCAN PRINTS BLOCKS-DOMO
11	697	S266 S623 T18 S138 T155 S215 S247 T524 T631 T684 S4 S32 S113 S122 T219 T249 T332 T519 T606 T611 S619	N111 N533 N598	Transmembrane domains: L36-V54; S62-Y84 Y125-R142; S177-I192 S198-F214; F298-H320 I381-G398 Signal peptide: M1-W56 Prostanoid EP1 receptor: V360-S384; D110-R134 2 Poly-Immunoglobulin receptor: I64-N111; L162-A209		HMM SPSCAN PRINTS BLOCKS-DOMO

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Motifs, Signature Sequences, and Protein Domains	Homologous Sequences	Analytical Methods
12	325	S56 T185 T234 S289 S76 S211 T245 S248	N64 N287	Transmembrane domain: Q26-V44 Signal peptide: M1-S52 2 Poly-Immunoglobulin receptor: M1-P48; A22-K69 V95-G142; V118-G165	Non-CD4 glycoprotein gp120 receptor R32188	HMM BLAST SPSCAN BLOCKS-DOMO
13	369	T12 T69 T299 S312 S330 T346 S50 S92 T145	N10 N90 N297	Transmembrane domains: I144-L161; V196-L219 L264-Y283 Signal peptide: M1-G47 Prostaglandin D receptor: Y6-A20; L41-P58 L93-L104; I185-S200 P236-E259; P280-K291 2 Poly-Immunoglobulin receptor: T11-P58; N10-L57 R52-A99; S195-L225 7 Transmembrane receptor: G33-P280	DP prostanoïd receptor g940379	HMM BLAST SPSCAN PRINTS BLOCKS-DOMO PFAM

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Diseases, Disorders, or Conditions (Fraction of Total)	Vector
14	146-301	Lung (1.000)	Cancer (1.000)	pINCY
15	423-500	Fetal Thymus (0.333) Wrist Synovium (0.333) Seminal Vesicle (0.333)	Cancer (0.333) Cell Proliferation (0.333) Inflammation (0.333)	pINCY
16	94-138	Hematopoietic/Immune (0.636) Gastrointestinal (0.273)	Inflammation (0.636) Cancer (0.364)	PSPORT1
17	703-747	Nervous System (1.000)	Neurological (0.333) Trauma (0.333) Cancer (0.333)	PSPORT1
18	293-325 434-478	Cardiovascular (0.333) Developmental (0.167) Hematopoietic/Immune (0.167)	Cancer (0.833) Fetal (0.167)	pINCY
19	109-153 1339-1383	Gastrointestinal (0.333) Reproductive (0.333) Hematopoietic/Immune (0.250)	Cancer (0.500) Inflammation (0.250) Fetal (0.167)	pINCY
20	519-563	Hematopoietic/Immune (0.571) Cardiovascular (0.143) Reproductive (0.143)	Inflammation (0.357) Cancer (0.214) Trauma (0.143)	pINCY
21	319-360	Nervous (0.235) Cardiovascular (0.206) Reproductive (0.206)	Cancer and Cell Proliferation (0.529) Inflammation (0.412)	PBLUESCRIPT
22	558-599	Reproductive (0.361) Nervous (0.180) Cardiovascular (0.115)	Cancer and Cell Proliferation (0.689) Inflammation (0.311)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Diseases, Disorders, or Conditions (Fraction of Total)	Vector
23	8-47 900-940	Reproductive (0.280) Nervous (0.160) Gastrointestinal (0.133)	Cancer and Cell Proliferation (0.666) Inflammation (0.253)	pINCY
24	800-840	Reproductive (0.237) Nervous (0.186) Cardiovascular (0.153)	Cancer and Cell Proliferation (0.664) Trauma (0.186)	pINCY
25	770-814	Hematopoietic/Immune (0.333) Gastrointestinal (0.222) Cardiovascular (0.111) Endocrine (0.111) Nervous (0.111) Reproductive (0.111)	Inflammation (0.444) Fetal (0.222) Trauma (0.222)	pINCY
26	1078-1119	Nervous (0.500) Cardiovascular (0.250) Musculoskeletal (0.250)	Cancer (0.750) Trauma (0.250)	pINCY

Table 4

Polypeptide SEQ ID NO:	Library	Library Description
14	LUNGNOT20	This library was constructed using RNA isolated from right upper lobe lung tissue removed from a 61-year-old Caucasian male. Pathology indicated panacinar emphysema with blebs in the right anterior upper lobe and apex, as well as emphysema in the right posterior upper lobe. Patient history included angina pectoris and gastric ulcer. Family history included a subdural hemorrhage, cancer, atherosclerotic coronary artery disease, and pneumonia.
15	THYMFET03	This library was constructed using RNA isolated from thymus tissue removed from a premature Caucasian male fetus who died at birth.
16	LNODNOT02	This library was constructed using RNA isolated from the lymph node tissue of a 42-year-old Caucasian female who died of cardiac arrest.
17	SCORNON02	This normalized spinal cord library was constructed from 3.24 million independent clones from a spinal cord library. RNA was isolated from spinal cord tissue removed from a 71-year-old Caucasian male who died from respiratory arrest. Patient history included myocardial infarction, gangrene, and end stage renal disease. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9928).
18	BMARNOT03	This library was constructed using RNA isolated from left tibial bone marrow tissue of a 16-year-old Caucasian male during a partial left tibial osteotomy with free skin graft. Patient history included an abnormality of the red blood cells. Previous surgeries included bone and bone marrow biopsy and soft tissue excision. Family history included osteoarthritis.
19	BRSTTUT13	This library was constructed using RNA isolated from breast tumor tissue removed from a 46-year-old Caucasian female during a unilateral extended simple mastectomy with breast reconstruction. Pathology indicated an invasive grade 3 adenocarcinoma, ductal type with apocrine features and greater than 50% intraductal component. Patient history included breast cancer.

Table 4 (cont.)

Polypeptide SEQ ID NO:	Library	Library Description
20	LUNGNOT28	This library was constructed using RNA isolated from lung tissue removed from a 53-year-old male. Pathology for the associated tumor tissue indicated grade 4 adenocarcinoma.
21	LUNGNOT02	This library was constructed using RNA isolated from the lung tissue of a 47-year-old Caucasian male, who died of a subarachnoid hemorrhage.
22	BRAITUT12	This library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated grade 4 gemistocytic astrocytoma.
23	URETTUT01	This library was constructed using RNA isolated from right ureter tumor tissue of a 69-year-old Caucasian male during ureterectomy and lymph node excision. Pathology indicated invasive grade 3 transitional cell carcinoma. Patient history included benign colon neoplasm, asthma, emphysema, acute duodenal ulcer, and hyperplasia of the prostate. Family history included atherosclerotic coronary artery disease, congestive heart failure, and malignant lung neoplasm.
24	BRSTNOT07	This library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
25	SPLNNOT09	This library was constructed using RNA isolated from diseased spleen tissue removed from a 22-year-old Caucasian male during a total splenectomy. Pathology indicated Gaucher's disease with marked splenomegaly. Patient history included thyroid disorders and type 1 Gaucher's disease.

Table 4 (cont.)

Polypeptide SEQ ID NO:	Library	Library Description
26	BRONNOT01	This library was constructed using RNA isolated from bronchial tissue removed from a 15-year-old Caucasian male.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	<p>ESTx: Probability value= 1.0E-8 or less</p> <p>Full Length sequences: Probability value= 1.0E-10 or less</p>
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	<p>ESTx: fasta E value=1.06E-6</p> <p>Assembled ESTx: fasta Identity= 95% or greater and</p> <p>Match length=200 bases or greater;</p> <p>fastx E value=1.0E-8 or less</p> <p>Full Length sequences:</p> <p>fastx score=100 or greater</p>
BLIMPS	A BLOCKS IMPROVED Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	<p>Score=1000 or greater.</p> <p>Ratio of Score/Strength = 0.75 or larger; and, if applicable,</p> <p>Probability value= 1.0E-3 or less</p>
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score ₂ GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm. useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <i>supra</i> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, and fragments thereof.
2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
7. A method for detecting a polynucleotide, the method comprising the steps of:
 - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:14-26 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 90% polynucleotide

sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

5

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

10

14. A method for producing a polypeptide, the method comprising the steps of:

a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

20

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of HCSR, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of HCSR, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

30

SEQUENCE LISTING

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 TANG, Y. Tom
 CORLEY, Neil C.
 GUEGLER, Karl J.
 YUE, Henry
 BAUGHN, Mariah R.
 LAL, Preeti
 HILLMAN, Jennifer L.
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Gly Met Ser His Gly Lys Leu Cys Arg Leu His Gln Ala Pro Thr
65 70 75
Ala Arg Gly Gly Gly Ala Leu Leu Val Cys Ala Ala Tyr Arg Arg
80 85 90
His Val Glu Leu Arg Ala Pro Arg Val Gly Arg His Ser Ser Leu
95 100 105
Arg Arg Ser Ala Ile Ser Pro Cys His Pro His Gln
110 115

<210> 6
 <211> 455
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2851578CD1

<400> 6
Met Glu Gly Gly Arg Ala Ala Gly Phe Pro Leu Ala Cys Lys Gln
1 5 10 15
Glu His Arg Val Phe Leu Ser Gly Cys Glu Asn Ala Asp Glu Asn
20 25 30
Pro Arg Met Leu Cys His Arg Gly Gly Gln Leu Ile Val Pro Ile
35 40 45
Ile Pro Leu Cys Pro Glu His Ser Cys Arg Gly Arg Arg Leu Gln
50 55 60
Asn Leu Leu Ser Gly Pro Trp Pro Lys Gln Pro Met Glu Leu His
65 70 75
Asn Leu Ser Ser Pro Ser Pro Ser Leu Ser Ser Ser Val Leu Pro
80 85 90
Pro Ser Phe Ser Pro Ser Pro Ser Ser Ala Pro Ser Ala Phe Thr
95 100 105
Thr Val Gly Gly Ser Ser Gly Gly Pro Cys His Pro Thr Ser Ser
110 115 120
Ser Leu Val Ser Ala Phe Leu Ala Pro Ile Leu Ala Leu Glu Phe
125 130 135
Val Leu Gly Leu Val Gly Asn Ser Leu Ala Leu Phe Ile Phe Cys
140 145 150
Ile His Thr Arg Pro Trp Thr Ser Asn Thr Val Phe Leu Val Ser
155 160 165
Leu Val Ala Ala Asp Phe Leu Leu Ile Ser Asn Leu Pro Leu Arg
170 175 180
Val Asp Tyr Tyr Leu Leu His Glu Thr Trp Arg Phe Gly Ala Ala
185 190 195
Ala Cys Lys Val Asn Leu Phe Met Leu Ser Thr Asn Arg Thr Ala
200 205 210
Ser Val Val Phe Leu Thr Ala Ile Ala Leu Asn Arg Tyr Leu Lys
215 220 225
Val Val Gln Pro His His Val Leu Ser Arg Ala Ser Val Gly Ala
230 235 240
Ala Ala Arg Val Ala Gly Gly Leu Trp Val Gly Ile Leu Leu Leu
245 250 255
Asn Gly His Leu Leu Leu Ser Thr Phe Ser Gly Pro Ser Cys Leu
260 265 270
Ser Tyr Arg Val Gly Thr Lys Pro Ser Ala Ser Leu Arg Trp His
275 280 285
Gln Ala Leu Tyr Leu Leu Glu Phe Phe Leu Pro Leu Ala Leu Ile
290 295 300
Leu Phe Ala Ile Val Ser Ile Gly Leu Thr Ile Arg Asn Arg Gly
305 310 315
Leu Gly Gly Gln Ala Gly Pro Gln Arg Ala Met Arg Val Leu Ala
320 325 330
Met Val Val Ala Val Tyr Thr Ile Cys Phe Leu Pro Ser Ile Ile
335 340 345
Phe Gly Met Ala Ser Met Val Ala Phe Trp Leu Ser Ala Cys Arg
350 355 360
Ser Leu Asp Leu Cys Thr Gln Leu Phe His Gly Ser Leu Ala Phe
365 370 375
Thr Tyr Leu Asn Ser Val Leu Asp Pro Val Leu Tyr Cys Phe Ser
380 385 390
Ser Pro Asn Phe Leu His Gln Ser Arg Ala Leu Leu Gly Leu Thr
395 400 405

Arg Gly Arg Gln Gly Pro Val Ser Asp Glu Ser Ser Tyr Gln Pro
 410 415 420
 Ser Arg Gln Trp Arg Tyr Arg Glu Ala Ser Arg Lys Ala Glu Ala
 425 430 435
 Ile Gly Lys Leu Lys Val Gln Gly Glu Val Ser Leu Glu Lys Glu
 440 445 450

Gly Ser Ser Gln Gly
 455

<210> 7

<211> 453

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3393757CD1

<400> 7

Met Gln Leu Asp Trp Asn Gln Ala Gln Lys Ser Gly Asp Pro Gly
 1 5 10 15
 Pro Ser Val Val Gly Leu Val Ser Ile Pro Gly Met Gly Lys Leu
 20 25 30
 Leu Ala Glu Ala Pro Leu Val Leu Glu Pro Glu Lys Gln Met Leu
 35 40 45
 Leu His Glu Thr His Gln Gly Leu Leu Gln Asp Gly Ser Pro Ile
 50 55 60
 Leu Leu Ser Asp Val Ile Ser Ala Phe Leu Ser Asn Asn Asp Thr
 65 70 75
 Gln Asn Leu Ser Ser Pro Val Thr Phe Thr Phe Ser His Arg Ser
 80 85 90
 Val Ile Pro Arg Gln Lys Val Leu Cys Val Phe Trp Glu His Gly
 95 100 105
 Gln Asn Gly Cys Gly His Trp Ala Thr Thr Gly Cys Ser Thr Ile
 110 115 120
 Gly Thr Arg Asp Thr Ser Thr Ile Cys Arg Cys Thr His Leu Ser
 125 130 135
 Ser Phe Ala Val Leu Met Ala His Tyr Asp Val Gln Glu Glu Asp
 140 145 150
 Pro Val Leu Thr Val Ile Thr Tyr Met Gly Leu Ser Val Ser Leu
 155 160 165
 Leu Cys Leu Leu Leu Ala Ala Leu Thr Phe Leu Leu Cys Lys Ala
 170 175 180
 Ile Gln Asn Thr Ser Thr Ser Leu His Leu Gln Leu Ser Leu Cys
 185 190 195
 Leu Phe Leu Ala His Leu Leu Phe Leu Val Ala Ile Asp Gln Thr
 200 205 210
 Gly His Lys Val Leu Cys Ser Ile Ile Ala Gly Thr Leu His Tyr
 215 220 225
 Leu Tyr Leu Ala Thr Leu Thr Trp Met Leu Leu Glu Ala Leu Tyr
 230 235 240
 Leu Phe Leu Thr Ala Arg Asn Leu Thr Val Val Asn Tyr Ser Ser
 245 250 255


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Ile Asn Arg Phe Met Lys Lys Leu Met Phe Pro Val Gly Tyr Gly
260 265 270
Val Pro Ala Val Thr Val Ala Ile Ser Ala Ala Ser Arg Pro His
275 280 285
Leu Tyr Gly Thr Pro Ser Arg Cys Trp Leu Gln Pro Glu Lys Gly
290 295 300
Phe Ile Trp Gly Phe Leu Gly Pro Val Cys Ala Ile Phe Ser Val
305 310 315
Asn Leu Val Leu Phe Leu Val Thr Leu Trp Ile Leu Lys Asn Arg
320 325 330
Leu Ser Ser Leu Asn Ser Glu Val Ser Thr Leu Arg Asn Thr Arg
335 340 345
Met Leu Ala Phe Lys Ala Thr Ala Gln Leu Phe Ile Leu Gly Cys
350 355 360
Thr Trp Cys Leu Gly Ile Leu Gln Val Gly Pro Ala Ala Arg Val
365 370 375
Met Ala Tyr Leu Phe Thr Ile Ile Asn Ser Leu Gln Gly Val Phe
380 385 390
Ile Phe Leu Val Tyr Cys Leu Leu Ser Gln Gln Val Arg Glu Gln
395 400 405
Tyr Gly Lys Trp Ser Lys Gly Ile Arg Lys Leu Lys Thr Glu Ser
410 415 420
Glu Met His Thr Leu Ser Ser Ser Ala Lys Ala Asp Thr Ser Lys
425 430 435
Pro Ser Thr Val Arg Ser Arg Ile Ala Pro Glu His Phe Thr Asn
440 445 450
Arg Pro Thr

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<210> 8
<211> 442
<212> PRT
<213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte ID No: 312256CD1

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<400> 8
Met Ala Ser Val Val Leu Pro Ser Gly Ser Gln Cys Ala Ala Ala
1 5 10 15
Ala Ala Ala Ala Ala Pro Pro Gly Leu Arg Leu Arg Leu Leu Leu
20 25 30
Leu Leu Phe Ser Ala Ala Ala Leu Ile Pro Thr Gly Asp Gly Gln
35 40 45
Asn Leu Phe Thr Lys Asp Val Thr Val Ile Glu Gly Glu Val Ala
50 55 60
Thr Ile Ser Cys Gln Val Asn Lys Ser Asp Asp Ser Val Ile Gln
65 70 75
Leu Leu Asn Pro Asn Arg Gln Thr Ile Tyr Phe Arg Asp Phe Arg
80 85 90
Pro Leu Lys Asp Ser Arg Phe Gln Leu Leu Asn Phe Ser Ser Ser
95 100 105
Glu Leu Lys Val Ser Leu Thr Asn Val Ser Ile Ser Asp Glu Gly

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110	115	120
Arg Tyr Phe Cys Gln Leu Tyr Thr Asp	Pro Pro Gln Glu Ser Tyr	
125	130	135
Thr Thr Ile Thr Val Leu Val Pro Pro	Arg Asn Leu Met Ile Asp	
140	145	150
Ile Gln Lys Asp Thr Ala Val Glu Gly	Glu Glu Ile Glu Val Asn	
155	160	165
Cys Thr Ala Met Ala Ser Lys Pro Ala	Thr Thr Ile Arg Trp Phe	
170	175	180
Lys Gly Asn Thr Glu Leu Lys Gly Lys	Ser Glu Val Glu Glu Trp	
185	190	195
Ser Asp Met Tyr Thr Val Thr Ser Gln	Leu Met Leu Lys Val His	
200	205	210
Lys Glu Asp Asp Gly Val Pro Val Ile	Cys Gln Val Glu His Pro	
215	220	225
Ala Val Thr Gly Asn Leu Gln Thr Gln	Arg Tyr Leu Glu Val Gln	
230	235	240
Tyr Lys Pro Gln Val His Ile Gln Met	Thr Tyr Pro Leu Gln Gly	
245	250	255
Leu Thr Arg Glu Gly Asp Ala Leu Glu	Leu Thr Cys Glu Ala Ile	
260	265	270
Gly Lys Pro Gln Pro Val Met Val Thr	Trp Val Arg Val Asp Asp	
275	280	285
Glu Met Pro Gln His Ala Val Leu Ser	Gly Pro Asn Leu Phe Ile	
290	295	300
Asn Asn Leu Asn Lys Thr Asp Asn Gly	Thr Tyr Arg Cys Glu Ala	
305	310	315
Ser Asn Ile Val Gly Lys Ala His Ser	Asp Tyr Met Leu Tyr Val	
320	325	330
Tyr Asp Pro Pro Thr Thr Ile Pro Pro	Pro Thr Thr Thr Thr Thr	
335	340	345
Thr Thr Thr Thr Thr Thr Thr Thr Ile	Leu Thr Ile Ile Thr Asp	
350	355	360
Ser Arg Ala Gly Glu Glu Gly Ser Ile	Arg Ala Val Asp His Ala	
365	370	375
Val Ile Gly Gly Val Val Ala Val Val	Val Phe Ala Met Leu Cys	
380	385	390
Leu Leu Ile Ile Leu Gly Arg Tyr Phe	Ala Arg His Lys Gly Thr	
395	400	405
Tyr Phe Thr His Glu Ala Lys Gly Ala	Asp Asp Ala Ala Asp Ala	
410	415	420
Asp Thr Ala Ile Ile Asn Ala Glu Gly	Gly Gln Asn Asn Ser Glu	
425	430	435
Glu Lys Lys Glu Tyr Phe Ile		
440		

<210> 9

<211> 382

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1615704CD1

<400> 9

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Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Ser Val Leu
  1          5          10          15
Met Gly Leu Val Leu Ile Cys Val Cys Ser Lys Thr His Ser Leu
  20          25          30
Lys Gly Leu Ala Arg Gly Gly Ala Gln Ile Phe Ser Cys Ile Ile
  35          40          45
Pro Glu Cys Leu Gln Arg Ala Val His Gly Leu Leu His Tyr Leu
  50          55          60
Phe His Thr Arg Asn His Thr Phe Ile Val Leu His Leu Val Leu
  65          70          75
Gln Gly Met Val Tyr Thr Glu Tyr Thr Trp Glu Val Phe Gly Tyr
  80          85          90
Cys Gln Glu Leu Glu Leu Ser Leu His Tyr Leu Leu Leu Pro Tyr
  95          100         105
Leu Leu Leu Gly Val Asn Leu Phe Phe Phe Thr Leu Thr Cys Gly
  110         115         120
Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu Leu Phe Leu
  125         130         135
His Val Tyr Glu Phe Asp Glu Val Met Phe Pro Lys Asn Val Arg
  140         145         150
Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Lys His Cys
  155         160         165
Ser Glu Cys Gly Ser Arg Asp Ser Ser Gly Thr Ser Asn Ser Thr
  170         175         180
Cys Val Gly Phe Val Cys Glu Gly Met Phe Pro Glu Ser Glu Ser
  185         190         195
Arg Ala Ser Ser Pro Pro Asp Met Val Cys Val Thr Trp Cys Val
  200         205         210
His Arg Phe Asp His His Cys Val Trp Val Asn Asn Cys Ile Gly
  215         220         225
Ala Trp Asn Ile Arg Tyr Phe Leu Ile Tyr Val Leu Thr Leu Thr
  230         235         240
Ala Ser Ala Ala Thr Val Ala Ile Val Ser Thr Thr Phe Leu Val
  245         250         255
His Leu Val Val Met Ser Asp Leu Tyr Gln Glu Thr Tyr Ile Asp
  260         265         270
Asp Leu Gly His Leu His Val Met Asp Thr Val Phe Leu Ile Gln
  275         280         285
Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu Gly Phe
  290         295         300
Val Val Val Leu Ser Phe Leu Leu Gly Gly Tyr Leu Leu Phe Val
  305         310         315
Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
  320         325         330
Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro
  335         340         345
Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly
  350         355         360

Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys
  365         370         375
His Glu Arg Lys Lys Gln Glu
  380

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<210> 10
 <211> 257
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1659465CD1

<400> 10
 Met Ala Ser Lys Ile Gly Ser Arg Arg Trp Met Leu Gln Leu Ile
 1 5 10 15
 Met Gln Leu Gly Ser Val Leu Leu Thr Arg Cys Pro Phe Trp Gly
 20 25 30
 Cys Phe Ser Gln Leu Met Leu Tyr Ala Glu Arg Ala Glu Ala Arg
 35 40 45
 Arg Lys Pro Asp Ile Pro Val Pro Tyr Leu Tyr Phe Asp Met Gly
 50 55 60
 Ala Ala Val Leu Cys Ala Ser Phe Met Ser Phe Gly Val Lys Arg
 65 70 75
 Arg Trp Phe Ala Leu Gly Ala Ala Leu Gln Leu Ala Ile Ser Thr
 80 85 90
 Tyr Ala Ala Tyr Ile Gly Gly Tyr Val His Tyr Gly Asp Trp Leu
 95 100 105
 Lys Val Arg Met Tyr Ser Arg Thr Val Ala Ile Ile Gly Gly Phe
 110 115 120
 Leu Val Leu Ala Ser Gly Ala Gly Glu Leu Tyr Arg Arg Lys Pro
 125 130 135
 Arg Ser Arg Ser Leu Gln Ser Thr Gly Gln Val Phe Leu Gly Ile
 140 145 150
 Tyr Leu Ile Cys Val Ala Tyr Ser Leu Gln His Ser Lys Glu Asp
 155 160 165
 Arg Leu Ala Tyr Leu Asn His Leu Pro Gly Gly Glu Leu Met Ile
 170 175 180
 Gln Leu Phe Phe Val Leu Tyr Gly Ile Leu Ala Leu Ala Phe Leu
 185 190 195
 Ser Gly Tyr Tyr Val Thr Leu Ala Ala Gln Ile Leu Ala Val Leu
 200 205 210
 Leu Pro Pro Val Met Leu Leu Ile Asp Gly Asn Val Ala Tyr Trp
 215 220 225
 His Asn Thr Arg Arg Val Glu Phe Trp Asn Gln Met Lys Leu Leu
 230 235 240
 Gly Glu Ser Val Gly Ile Phe Gly Thr Ala Val Ile Leu Ala Thr
 245 250 255
 Asp Gly

<210> 11
 <211> 697
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature

<223> Incyte ID No: 2120743CD1

<400> 11

Met	Cys	Lys	Ser	Leu	Arg	Tyr	Cys	Phe	Ser	His	Cys	Leu	Tyr	Leu	1	5	10	15
Ala	Met	Thr	Arg	Leu	Glu	Glu	Val	Asn	Arg	Glu	Val	Asn	Met	His	20	25	30	
Ser	Ser	Val	Arg	Tyr	Leu	Gly	Tyr	Leu	Ala	Arg	Ile	Asn	Leu	Leu	35	40	45	
Val	Ala	Ile	Cys	Leu	Gly	Leu	Tyr	Val	Arg	Trp	Glu	Lys	Thr	Ala	50	55	60	
Asn	Ser	Leu	Ile	Leu	Val	Ile	Phe	Ile	Leu	Gly	Leu	Phe	Val	Leu	65	70	75	
Gly	Ile	Ala	Ser	Ile	Leu	Tyr	Tyr	Tyr	Phe	Ser	Met	Glu	Ala	Ala	80	85	90	
Ser	Leu	Ser	Leu	Ser	Asn	Leu	Trp	Phe	Gly	Phe	Leu	Leu	Gly	Leu	95	100	105	
Leu	Cys	Phe	Leu	Asp	Asn	Ser	Ser	Phe	Lys	Asn	Asp	Val	Lys	Glu	110	115	120	
Glu	Ser	Thr	Lys	Tyr	Leu	Leu	Leu	Thr	Ser	Ile	Val	Leu	Arg	Ile	125	130	135	
Leu	Cys	Ser	Leu	Val	Glu	Arg	Ile	Ser	Gly	Tyr	Val	Arg	His	Arg	140	145	150	
Pro	Thr	Leu	Leu	Thr	Thr	Val	Glu	Phe	Leu	Glu	Leu	Val	Gly	Phe	155	160	165	
Ala	Ile	Ala	Ser	Thr	Thr	Met	Leu	Val	Glu	Lys	Ser	Leu	Ser	Val	170	175	180	
Ile	Leu	Leu	Val	Val	Ala	Leu	Ala	Met	Leu	Ile	Ile	Asp	Leu	Arg	185	190	195	
Met	Lys	Ser	Phe	Leu	Ala	Ile	Pro	Asn	Leu	Val	Ile	Phe	Ala	Val	200	205	210	
Leu	Leu	Phe	Phe	Ser	Ser	Leu	Glu	Thr	Pro	Lys	Asn	Pro	Ile	Ala	215	220	225	
Phe	Ala	Cys	Phe	Phe	Ile	Cys	Leu	Ile	Thr	Asp	Pro	Phe	Leu	Asp	230	235	240	
Ile	Tyr	Phe	Ser	Gly	Leu	Ser	Val	Thr	Glu	Arg	Trp	Lys	Pro	Phe	245	250	255	
Leu	Tyr	Arg	Gly	Arg	Ile	Cys	Arg	Arg	Leu	Ser	Val	Val	Phe	Ala	260	265	270	
Gly	Met	Ile	Glu	Leu	Thr	Phe	Phe	Ile	Leu	Ser	Ala	Phe	Lys	Leu	275	280	285	
Arg	Asp	Thr	His	Leu	Trp	Tyr	Phe	Val	Ile	Pro	Gly	Phe	Ser	Ile	290	295	300	
Phe	Gly	Ile	Phe	Trp	Met	Ile	Cys	His	Ile	Ile	Phe	Leu	Leu	Thr	305	310	315	
Leu	Trp	Gly	Phe	His	Thr	Lys	Leu	Asn	Asp	Cys	His	Lys	Val	Tyr	320	325	330	
Phe	Thr	His	Arg	Thr	Asp	Tyr	Asn	Ser	Leu	Asp	Arg	Ile	Met	Ala	335	340	345	
Ser	Lys	Gly	Met	Arg	His	Phe	Cys	Leu	Ile	Ser	Glu	Gln	Leu	Val	350	355	360	
Phe	Phe	Ser	Leu	Leu	Ala	Thr	Ala	Ile	Leu	Gly	Ala	Val	Ser	Trp	365	370	375	
Gln	Pro	Thr	Asn	Gly	Ile	Phe	Leu	Ser	Met	Phe	Leu	Ile	Val	Leu	380	385	390	

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Pro Leu Glu Ser Met Ala His Gly Leu Phe His Glu Leu Gly Asn
      395                      400                      405
Cys Leu Gly Gly Thr Ser Val Gly Tyr Ala Ile Val Ile Pro Thr
      410                      415                      420
Asn Phe Cys Ser Pro Asp Gly Gln Pro Thr Leu Leu Pro Pro Glu
      425                      430                      435
His Val Gln Glu Leu Asn Leu Arg Ser Thr Gly Met Leu Asn Ala
      440                      445                      450
Ile Gln Arg Phe Phe Ala Tyr His Met Ile Glu Thr Tyr Gly Cys
      455                      460                      465
Asp Tyr Ser Thr Ser Gly Leu Ser Phe Asp Thr Leu His Ser Lys
      470                      475                      480
Leu Lys Ala Phe Leu Glu Leu Arg Thr Val Asp Gly Pro Arg His
      485                      490                      495
Asp Thr Tyr Ile Leu Tyr Tyr Ser Gly His Thr His Gly Thr Gly
      500                      505                      510
Glu Trp Ala Leu Ala Gly Gly Asp Thr Leu Arg Leu Asp Thr Leu
      515                      520                      525
Ile Glu Trp Trp Arg Glu Lys Asn Gly Ser Phe Cys Ser Arg Leu
      530                      535                      540
Ile Ile Val Leu Asp Ser Glu Asn Ser Thr Pro Trp Val Lys Glu
      545                      550                      555
Val Arg Lys Ile Asn Asp Gln Tyr Ile Ala Val Gln Gly Ala Glu
      560                      565                      570
Leu Ile Lys Thr Val Asp Ile Glu Glu Ala Asp Pro Pro Gln Leu
      575                      580                      585
Gly Asp Phe Thr Lys Asp Trp Val Glu Tyr Asn Cys Asn Ser Ser
      590                      595                      600
Asn Asn Ile Cys Trp Thr Glu Lys Gly Arg Thr Val Lys Ala Val
      605                      610                      615
Tyr Gly Val Ser Lys Arg Trp Ser Asp Tyr Thr Leu His Leu Pro
      620                      625                      630
Thr Gly Ser Asp Val Ala Lys His Trp Met Leu His Phe Pro Arg
      635                      640                      645
Ile Thr Tyr Pro Leu Val His Leu Ala Asn Trp Leu Cys Gly Leu
      650                      655                      660
Asn Leu Phe Trp Ile Cys Lys Thr Cys Phe Arg Cys Leu Lys Arg
      665                      670                      675
Leu Lys Met Ser Trp Phe Leu Pro Thr Val Leu Asp Thr Gly Gln
      680                      685                      690
Gly Phe Lys Leu Val Lys Ser
      695

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<210> 12

<211> 325

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3344986CD1

<400> 12

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Met Ser Asp Ser Lys Glu Pro Arg Val Gln Gln Leu Gly Leu Leu
  1              5              10              15

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Gly Cys Leu Gly His Gly Ala Leu Val Leu Gln Leu Leu Ser Phe		
	20	25 30
Met Leu Leu Ala Gly Val Leu Val Ala Ile Leu Val Gln Val Ser		
	35	40 45
Lys Val Pro Ser Ser Leu Ser Gln Glu Gln Ser Glu Gln Asp Ala		
	50	55 60
Ile Tyr Gln Asn Leu Thr Gln Leu Lys Ala Ala Val Gly Glu Leu		
	65	70 75
Ser Glu Lys Ser Lys Leu Gln Glu Ile Tyr Gln Glu Leu Thr Gln		
	80	85 90
Leu Lys Ala Ala Val Gly Glu Leu Pro Glu Lys Ser Lys Leu Gln		
	95	100 105
Glu Ile Tyr Gln Glu Leu Thr Arg Leu Lys Ala Ala Val Gly Glu		
	110	115 120
Leu Pro Glu Lys Ser Lys Leu Gln Glu Ile Tyr Gln Glu Leu Thr		
	125	130 135
Arg Leu Lys Ala Ala Val Gly Glu Leu Pro Glu Lys Ser Lys Leu		
	140	145 150
Gln Glu Ile Tyr Gln Glu Leu Thr Arg Leu Lys Ala Ala Val Gly		
	155	160 165
Glu Leu Pro Asp Gln Ser Lys Gln Gln Gln Ile Tyr Gln Glu Leu		
	170	175 180
Thr Asp Leu Lys Thr Ala Phe Glu Arg Leu Cys Arg His Cys Pro		
	185	190 195
Lys Asp Trp Thr Phe Phe Gln Gly Asn Cys Tyr Phe Met Ser Asn		
	200	205 210
Ser Gln Arg Asn Trp His Asp Ser Val Thr Ala Cys Gln Glu Val		
	215	220 225
Arg Ala Gln Leu Val Val Ile Lys Thr Ala Glu Glu Gln Asn Phe		
	230	235 240
Leu Gln Leu Gln Thr Ser Arg Ser Asn Arg Phe Ser Trp Met Gly		
	245	250 255
Leu Ser Asp Leu Asn Gln Glu Gly Thr Trp Gln Trp Val Asp Gly		
	260	265 270
Ser Pro Leu Ser Pro Ser Phe Gln Arg Tyr Trp Asn Ser Gly Glu		
	275	280 285
Pro Asn Asn Ser Gly Asn Glu Asp Cys Ala Glu Phe Ser Gly Ser		
	290	295 300
Gly Trp Asn Asp Asn Arg Cys Asp Val Asp Asn Tyr Trp Ile Cys		
	305	310 315
Lys Lys Pro Ala Ala Cys Phe Arg Asp Glu		
	320	325

<210> 13

<211> 369

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3576503CD1

<400> 13

Met Lys Ser Pro Phe Tyr Arg Cys Gln Asn Thr Thr Ser Val Glu

1	5	10	15
Lys Gly Asn Ser	Ala Val Met Gly Gly	Val Leu Phe Ser Thr	Gly
20	25	30	
Leu Leu Gly Asn	Leu Leu Ala Leu Gly	Leu Leu Ala Arg Ser	Gly
35	40	45	
Leu Gly Trp Cys	Ser Arg Arg Pro Leu Arg	Pro Leu Pro Ser	Val
50	55	60	
Phe Tyr Met Leu	Val Cys Gly Leu Thr	Val Thr Asp Leu Leu	Gly
65	70	75	
Lys Cys Leu Leu	Ser Pro Val Val Leu Ala	Ala Tyr Ala Gln Asn	
80	85	90	
Arg Ser Leu Arg	Val Leu Ala Pro Ala	Leu Asp Asn Ser Leu	Cys
95	100	105	
Gln Ala Phe Ala	Phe Phe Met Ser Phe	Phe Gly Leu Ser Ser	Thr
110	115	120	
Leu Gln Leu Leu	Ala Met Ala Leu Glu	Cys Trp Leu Ser Leu	Gly
125	130	135	
His Pro Phe Phe	Tyr Arg Arg His Ile	Thr Leu Arg Leu Gly	Ala
140	145	150	
Leu Val Ala Pro	Val Val Ser Ala Phe	Ser Leu Ala Phe Cys	Ala
155	160	165	
Leu Pro Phe Met	Gly Phe Gly Lys Phe	Val Gln Tyr Cys Pro	Gly
170	175	180	
Thr Trp Cys Phe	Ile Gln Met Val His	Glu Glu Gly Ser Leu	Ser
185	190	195	
Val Leu Gly Tyr	Ser Val Leu Tyr Ser	Ser Leu Met Ala Leu	Leu
200	205	210	
Val Leu Ala Thr	Val Leu Cys Asn Leu	Gly Ala Met Arg Asn	Leu
215	220	225	
Tyr Ala Met His	Arg Arg Leu Gln Arg	His Pro Arg Ser Cys	Thr
230	235	240	
Arg Asp Cys Ala	Glu Pro Arg Ala Asp	Gly Arg Glu Ala Ser	Pro
245	250	255	
Gln Pro Leu Glu	Glu Leu Asp His Leu	Leu Leu Leu Ala Leu	Met
260	265	270	
Thr Val Leu Phe	Thr Met Cys Ser Leu	Pro Val Ile Tyr Arg	Ala
275	280	285	
Tyr Tyr Gly Ala	Phe Lys Asp Val Lys	Glu Lys Asn Arg Thr	Ser
290	295	300	
Glu Glu Pro Glu	Arg Pro Pro Ser Leu	Ala Ile Ser Ile Cys	Asp
305	310	315	
Val Asn Cys Gly	Pro Leu Asp Ser Tyr	His Phe Gln Ile Ser	Ser
320	325	330	
Ile Ser Asp Ile	Phe Ser Gln Asp Phe	Ser Leu Asp Leu Leu	Gly
335	340	345	
Thr Gly Ala Asp	Ala Ala Ile Pro Leu	Thr Trp Asn Pro Val	Cys
350	355	360	
Asp Ser Val Phe	His Ser Val Val Ser		
365			

<210> 14

<211> 572

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2355971CB1

<400> 14

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gcgagcagc ccgaggcggg gcagcctccc ggagcagcgc cgcgcagagc ccgggacaat 60
ggggcccgcg cggctgctgc tgggtggccgc ctgcttcagt ctgtgcggcc cgctgttgc 120
tgcccgaccc cgggcccgcg gccaggtga gagatgcacg ggaatggggg gcgcggggcg 180
agggacgccc aggggagact gcgggggtca ctgttgcgac ttctctcac cctgcctca 240
gtttcctccg aaagccaaac tggcatttgg gctgagatct ggagttttt ccagtcacgt 300
ttaggtgggg cgtgccaccc ccttcgttgg cacagccgat gccccttgg actcgatctt 360
ggagggtgca gcccgctgc aacggggtgt tggatatgga ggaagatgga gcggaagccc 420
ctgggggagc ctgcagtcct gcgttgaat tgtcaacaaa accgtttctt cccaaggacc 480
aaccacaaa aaggaaaagc ttctcaagtt ggtcccaacc aattaaacgt ttcggatctt 540
ttaaaaaaac aaaaaaccaa aaggggcggg cc 572

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<210> 15

<211> 517

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2917059CB1

<400> 15

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2053

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, C07K 14/705, C12Q 1/68, A61K 38/17, C07K 16/18		A3	(11) International Publication Number: WO 00/28032
			(43) International Publication Date: 18 May 2000 (18.05.00)
(21) International Application Number: PCT/US99/26742		(71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).	
(22) International Filing Date: 12 November 1999 (12.11.99)		(72) Inventors; and	
(30) Priority Data:		(75) Inventors/Applicants (for US only): TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). BANDMAN, Olga [US/US]; 366 Anna Avenue, Mountain View, CA 94043 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). AU-YOUNG, Janice [US/US]; 1419 Kains Avenue, Berkeley, CA 94702 (US).	
09/191,280 12 November 1998 (12.11.98) US Not furnished 12 November 1998 (12.11.98) US 09/206,647 7 December 1998 (07.12.98) US Not furnished 7 December 1998 (07.12.98) US 60/123,404 8 March 1999 (08.03.99) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications			
US 09/191,280 (CIP) Filed on 12 November 1998 (12.11.98) US Not furnished (CIP) Filed on 12 November 1998 (12.11.98) US 09/206,647 (CIP) Filed on 7 December 1998 (07.12.98) US Not furnished (CIP) Filed on 7 December 1998 (07.12.98) US 60/123,404 (CIP) Filed on 8 March 1999 (08.03.99)			
		(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).	
		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
		Published <i>With international search report.</i>	
		(88) Date of publication of the international search report: 16 November 2000 (16.11.00)	
(54) Title: HUMAN CELL SURFACE RECEPTOR PROTEINS			
(57) Abstract			
<p>The invention provides human cell surface receptor proteins (HCSRPs) and polynucleotides which identify and encode HCSRPs. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of HCSRPs.</p>			

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DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/26742

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 C12Q1/68 A61K38/17 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 18456 A (UNIVERSITY OF CALIFORNIA) 7 May 1998 (1998-05-07) the whole document, especially residues 1-29 in SEQ ID NO:7 ---	1-16,19
X	WO 92 14750 A (UNIVERSITY OF CALIFORNIA ;COR THERAPEUTICS INC) 3 September 1992 (1992-09-03) the whole document, especially nucleotides 166-312 in Figure 1A ---	1-16,19
X	WO 94 05695 A (UNIVERSITY OF NEW YORK) 17 March 1994 (1994-03-17) the whole document, especially sequence 31 in figure 8B(2) --- -/--	1,2,15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

B document member of the same patent family

Date of the actual completion of the international search

9 March 2000

Date of making of the international search report

25. 07. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

CUPIDO, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/26742

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>EMBL/GenBank/DDBJ databases SEQ ID AC008515:Homo sapiens chromosome 5 clone CTC-455F7 4 August 1999 DOE Joint Genome Institute XP002132666 compare nucleotides 40760-41260 with nucleotides 516-1 in SEQ ID NO:14 -----</p>	3-6,9-11

INTERNATIONAL SEARCH REPORT

In tional application No.
PCT/US 99/26742

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☒ Claims Nos.: 17,18 and 20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheets

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-20 (all partly)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-20 (all partly)

Polypeptide comprising an amino acid sequence of SEQ ID NO:1, fragments and variants thereof, polynucleotides encoding them, methods of detecting related sequences, vectors and cells comprising said sequences and their use to produce a polypeptide, corresponding pharmaceutical compositions and antibodies.

2. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:2

3. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:3

4. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:4

5. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:5

6. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:6

7. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:7

8. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:8

9. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:9

10. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:11

12. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:12

13. Claims: 1-20 (all partly)

Idem as subject 1 but limited to SEQ ID NO:13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17,18 and 20

Claims 17, 18 and in part 20 refer to an antagonist and agonist of the polypeptides without giving a true technical characterisation. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Articles 5 and 6 PCT). No meaningful search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/26742

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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